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Ⅳ. 研究成果の刊行物・別刷

5

Kaposi's Sarcoma-Associated Virus Governs Gene Expression Profiles Toward B Cell Transformation

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1. Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8) was found in patients' specimens as a causative agent of Kaposi's sarcoma by representational difference analysis (RDA) (Chang et al., 1994). Initially identified fragments by RDA were KS330Bam and KS631Bam, which showed a sequence similarity to a portion of the open reading frame (ORF) 26 open reading frame encoding the capsid protein VP23 of herpesvirus saimiri (HVS) and the amino acid sequence encoded by the corresponding BDLF1 ORF of Epstein-Barr virus (EBV), and to the tegment protein, ORF75 and also the tegment protein of EBV, BNRF1 (p140), respectively. The following full sequence analysis revealed that KSHV was belonging to the γ-herpesvirus subfamily, the genus rhadinovirus rather than lymphocryptic virus and could be a new oncogenic DNA virus (Moore et al., 1996; Russo et al., 1996).

KSHV is supposed to infect various kinds of tissue *in vitro* at least by using integrin αVβ3 as a receptor (Garrigues et al., 2008) and establishes latency in B cells (Chen and Lagunoff, 2005). KSHV has been reported to infect a primary endothelial cell and can transform it into a spindle cell which is a characteristic feature of the oncogenic activity of KSHV in endothelial cells (Lagunoff et al., 2002) However, it has not been revealed effective *in vitro* infection to primary peripheral blood mononuclear cells (PBMC), which of course include B cell, as EBV can form lymphoblastoid cell lines (LCL). Extensive studies so far have revealed that KSHV should be an etiologic agent for Kaposi's sarcoma (KS), multicentric Castleman's disease (MCD), and primary effusion lymphoma (PEL) (Hengge et al., 2002a; Hengge et al., 2002b).

It is quite a big question how oncogenic viruses are involved in their related cancers. Especially limited host ranges of viruses only infecting with humans make this question more unanswerable. One approach to get a hint about this question and solve it is to see gene expression profiles of viruses-associated tumors. Recently, we analyzed three types of typical lymphocyte-originated tumor cell lines-primary effusion lymphoma (PEL) cell lines,

T cell leukemia cell lines (TCL), Burkitt lymphoma (BL) cell lines-and two sets of PBMCs-in order to know how PEL was generated by searching characteristic gene expression profiles. Our approach, however, might be just to show typical gene expression profiles after establishment of PEL cell lines and it may be very difficult to account for viral pathogenesis only by gene expression profiles. Needless to say, we need an experimental model to observe the whole process from virus infection to cancer formation. In this chapter, we discuss about how KSHV is involved in PEL formation and what to do next to solve questions about viral oncogenesis.

2. Characteristic features of KSHV

KSHV is a γ-herpesvirus mentioned above and the genome is double stranded linearized DNA about 170kb long including GC-rich repetitious repeat called terminal sequences (TR), the unit of which is 801bp and repeated 30~50 times at the end of the genome though the sequence and the repeated unit might be different among clones. The unique region of the genome is about 140kb long and encodes more than 80 genes, most of which are lytic genes (Russo et al., 1996). The linearized genome is circularized at the TR after entry into cells and usually stealthies as an episome not going to full lytic replication.

2.1 KSHV life cycles

Like the other herpesviruses, KSHV has two typical life cycles called lytic infection (or reactivation from latency) and latent infection. Lytic infection/reactivation is a virus producing cycle and probably all viral genes are expressed from immediate early (IE), early (E) and late (L) genes in a cascade-like fashion. A key factor for lytic replication is Reactivation Transcription Activator (RTA) (Chen et al., 2001; Lukac et al., 1998; Sun et al., 1998). RTA is a very strong transactivator and trans-activates the other viral E genes such as *K-bZIP* (*K8*), *orf57*, *pan* including *kaposin* (*k12*), a latent gene, not only through specific binding sequences but also through an indirect mechanism (Sakakibara et al., 2001). When L genes are successfully expressed, it leads to explosive daughter virus production, which is a final end of the viral life cycle to disseminate viral infection and survive as its virus itself in nature.

On the other hand, latent infection is a viral stealthing state. The viral genome replicates according to the host cell cycle and is partitioned into divided cells at least in KSHV infected PEL cell lines (Ballestas, Chatis, and Kaye, 1999). The viral copy number per cell appears to be maintained at the same (Ueda et al., 2006). In this state, expressing viral genes are extremely limited to a few genes such latency-associated nuclear antigen (*lana*), viral cyclin (*v-cyc*), viral flip (*v-flip*), kaposin (*k12*) and viral interferon regulatory factor 3 (*v-irf-3*) (Paulose-Murphy et al., 2001). The former three genes are actually in one unit of gene (Fig. 1). *lana* and *v-cyc-v-flip* expression is regulated by alternative splicing. *v-cyc-v-flip* is in one transcript and v-FLIP is translated through internal ribosome entry site (IRES). Although *k12* is an independent gene, these four genes are present in one region and actively expressed. It remains to be solved how latent genes are regulated, since neighbor genes just upstream or downstream are tightly inactivated in a high density of genes in the genome. Epigenetic marking might be important to establish this state but it is unclear how such an effect itself is controlled (Toth et al., 2010). As for a virus, latency is a kind of poised state waiting for lytic replication, because it could be unfavorable for the virus to disseminate and expand its generation.

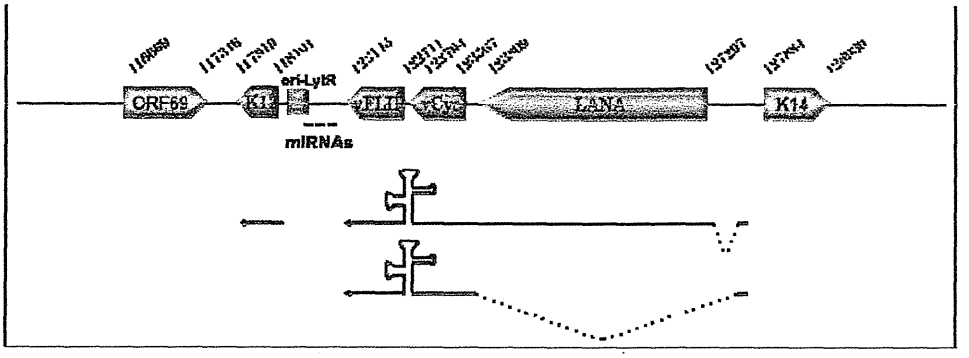

Fig. 1. The active gene locus around *lana*.

The viral latency might be the places for KSHV-associated malignancies mentioned below, since such malignancies usually show viral latent infection. And therefore, it seems to be quite important to understand what the viral latency is and it will give us hints to investigate functions of the viral latent genes products. Nevertheless, if the viral latenct genes products work for cellular immortalization and/or transformation, there may be more patients in KSHV infected people suffering from KSHV-associated malignancies. Thus, it should be kept in our mind to take this idea into consideration when thinking how KSHV is involved in cancer formation.

2.2 Latency-associated nuclear antigen (LANA)

LANA is one of the most actively produced viral factors and controls the viral latency. Though LANA seems to be a multifunctional protein, important functions of LANA in the latency are to support the viral genome replication, to partition the replicated viral genome and to maintain the same genome copy number per cell, and to regulate the viral genes expression (Han et al., 2010).

LANA has two binding sites called LANA binding sequences (LBS) in TR and replication origin of the KSHV genome in latency (ori-P) consists of the LBS and the following 32bp GC-rich segment (32GC) (Garber, Hu, and Renne, 2002; Garber et al., 2001). One of two LBS is required for the viral replication at least but it is not enough, i.e., 32GC is also required (Hu and Renne, 2005). Though it remains to be solved how the viral ori-P is determined among repeated TR sequences and how 32GC is functioning, LANA has been reported to interact with components of cellular replication machinery; origin recognition complex 1 to 6 (ORC1~ORC6) (Verma et al., 2006). Probably LANA binds with LBS and recruits ORCs on the ori-P to start replication. It is, however, very questionable whether LANA binds all ORCs at the same time. LANA also interacts with a histone acetyltransferase binding to ORC1 (HBO1) and epigenetic control around ori-P is may be more important (Stedman et al., 2004).

LANA is supposed to interact with a chromosome component, since the viral genomes are found in the vicinity of chromosomes and actually reported to bind with a histone such as H2B, and with Bub1, CENP-F and so on (Barbera et al., 2006; Xiao et al., 2010). Such interaction might account for the viral genome partition and maintenance, though the detail is unclear.

LANA regulates the viral genes expression and maybe cellular gene expression by interacting with components involved in heterochromatin formation such as heterochromatin protein 1 (HP1) and histone methyl transferase, suv39H1. LANA binds with LBS and recruits such

factors on the viral genome, which forms heterochromatin-like environment of the genome and as a whole inactive gene expression (Sakakibara et al., 2004).
Viral genes expressed in the latency might have oncogenic activities because KSHV-associated malignancies are usually in latency setting. Multifunctional LANA interacts with many cellular factors other than those mentioned above. Several mechanisms are thought how LANA works in the viral oncogenesis. LANA interacts with suppressive oncogenes such as p53 (Friborg et al., 1999) as the other oncogenic DNA viral genes products. We have confirmed that LANA interacts with p53 to degradade (Suzuki et al., 2010) but not pRb (our personal observation). It was also reported that LANA interacted with glycogen synthase kinase 3β (GSK3β) and blocked β-catenin degradation pathway that was promoted β-catenin phosphorylation by GSK3β (Liu et al., 2007). On the other hand, stably LANA expressing cells are, however, very difficult to establish, which means that LANA expression might give disadvantage for cell growth rather than cell growth promotion (our personal observation).

2.3 Viral cyclin (v-CYC)

KSHV encodes a cyclin D homologue termed v-cyclin, which is translated from alternatively spliced mRNA covering the *lana-v-cyc-v-flip* region (Li et al., 1997) (Fig. 1). v-CYC interacts with cyclin dependent kinase 6 (CDK6) and promotes G1-S progression (Godden-Kent et al., 1997; Swanton et al., 1997). The Cyclin D-CDK6 complex is to function to exit from G0 to G1 phase (Laman et al., 2001) and the v-cyc/CDK6 complex is resistant to inhibition by CDK inhibitors by p16, p21 and p27 (Jarviluoma et al., 2004). Thus, its real function has not been elucidated and it was reported that ectopic or overexpression of c-CYC evokes rather cell/DNA damage (Koopal et al., 2007).

2.4 Viral FLICE inhibitory protein (v-FLIP)

KSHV encoded *v-flip*, a homologue of cellular flip (*c-flip*) is expressed as co-transcript with *v-cyc* and translated via internal ribosome entry site (IRES). v-FLIP activates NF-kB to maintain PEL cell tumor phenotype (Guasparri, Keller, and Cesarman, 2004). Inhibition of NF-kB activity and knocking down v-FLIP lead to KSHV infected PEL cell death (Keller, Schattner, and Cesarman, 2000). NF-kB activity is also required for maintenance of KSHV latency (Ye et al., 2008) and v-FLIP, thus, may sustain the viral latency in B cells to stand by for oncogenic transformation and maintain the transformed phenotype (de Oliveira, Ballon, and Cesarman, 2010). Oncogenic activity of v-FLIP was also reported and in transgenic mice models, v-FLIP expression induces B cell transdifferentiation and tumorigenesis (Ballon et al., 2011). Furthermore, v-FLIP represses cell death with autophagy by interacting Atg3 (Lee et al., 2009).

2.5 Kaposin (K12)

Kaposin is a uniquely transcribed at the edge of the active transcription region of the KSHV genome (Li et al., 2002). There are three frames around this region and probably a major gene is so-called *kaposin B* whose C-terminal region is corresponding to K12 ORF. Open reading frame (ORF) of KAPOSIN B contains reiterated proline-rich, 23-amino acid direct repeats, since this region includes one of two ori-Lyt sequences (lytic replication origin) (Sadler et al., 1999). KAPOSIN B activates p38 mediated mitogen-activated protein kinase [MAPK]-associated protein kinase 2 (MK2) make AU-rich 3′ UTR containing mRNA stabilize (McCormick and Ganem, 2005). Activation of p38, on the other hand, was reported

to induce lytic cycle of the virus (Yoo et al., 2010). Thus, although there is a conflict in KAPOSIN B function in the KSHV latency, a lot of transcripts including T0.7 polyA (-) RNA and k12 mRNA are generated in this region.

2.6 KSHV microRNAs

Importantly, the region between ori-LytR and v-flip ORF is the region for the KSHV microRNA cluster and supplies with 17 mature microRNAs that do something in the viral latency (Boss, Plaisance, and Renne, 2009). As the cellular genomes produce various kinds of microRNA, especially DNA viruses also do (Cullen, 2009). Among them, some of them are targeting cellular genes; miR-K12-11 to BACH1, miR-K12-6-3p to THBS1, miR-K12-4-5p to Rbl2 (Lu et al., 2010), miR-K12-6 and miR-K12-11 to MAF (Hansen et al., 2010) and miR-K9 to *rta* to tune lytic reactivation finely (Lin et al., 2011), though their accurate transcription units or mechanisms have not been cleared. From now on, micro deletion mutant viruses in which each microRNA is precisely deleted will be required to understand their real sufficiency and necessity for their function, because gross deletion might have an effect on gene expression program around it.

2.7 v-IRF3 (K10.5)

KSHV encodes four genes with homology to human interferon regulatory factors (IRFs) called vIRF-1, -2, -3, -4 whose genes are clustered totally different region far from a *lana* including locus. And interestingly, one of them, vIRF-3 is expressed in the KSHV latency (Fig. 2). vIRF-3 was reported to be required for the survival of KSHV infected PELs (Wies et al., 2008), suggesting that it is a growth promoting factor by disabling type I and II interferon responses (Schmidt, Wies, and Neipel, 2011) , PML-mediated transcriptional repression of suvivin (Marcos-Villar et al., 2009), and inhibiting p53 function (Rivas et al., 2001) as well.

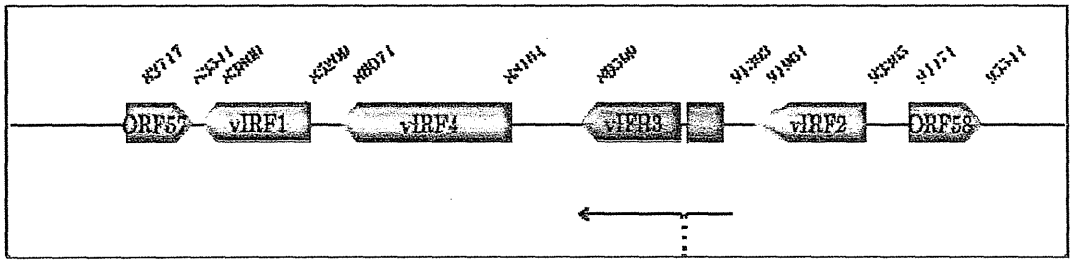

Fig. 2. vIRF region of the KSHV genome

2.8 Lytic viral genes and oncognesis

As mentioned, viral latency genes seems to have pivotal roles for the viral oncogenesis partly because the KSHV related malignancies usually happen in cells with the viral latency. Such genes products, however, do not have immortalizing and/or transforming activity either *in vitro* or *in vivo* except *v-flip* (Ballon et al., 2011). Putative KSHV oncogenes are rather encoded in lytic viral genes. KSHV *k1* and *v-gpcr* (*orf72*) showed real oncogenic activities (Mutlu et al., 2007). Thus, lytic genes should not be forgot and rather KSHV oncogenic activities should be considered on the pathway of reactivation from latency.

3. KSHV-associated malignancies

Since KHSV was found, extensive studies were performed to prove the involvement of KSHV in many cancers. Related diseases, however, are confined to a few cancers or cancer-like diseases; KS, MCD, and PEL. The other diseases such as multiple myeloma, sarcoidosis and primary pulmonary hypertension could not be KSHV-associated diseases. The former three diseases are certainly related to KSHV, though not hundred percent. Here, we would like to discuss about two B lymphocyte-originated tumors associated with KSHV infection.

3.1 Multicentric castleman's diesease (MCD)

MCD is a disease in which KSHV is involved. But KSHV is not necessarily associated in MCD and KSHV associated MCD is usually seen in AIDS setting (Dupin et al., 1999). KSHV-associated MCD is not associated with Epstein-Barr virus (EBV) (Oksenhendler et al., 1996). In contrast, PEL is usually coinfected with KSHV and EBV in vivo (Ansari et al., 1996). MCD is a B cell lymphoma morphologically resembling plasmablasts without undergoing a germinal center reaction (Parravicini et al., 2000). It is unclear how this disease is established but a KSHV viral load is a decisive factor for exacerbation of MCD (Grandadam et al., 1997) and thus KSHV should have a role in MCD pathogenesis.
High level interleukin 6 (IL-6) is a well-known fact in MCD and should do something in MCD pathogenesis (Oksenhendler et al., 1996). B cell markers, CD20 and the memory B cell marker CD27 are usually expressed, but B cell activation markers such as CD23, CD38 and CD30 are not. KSHV gene expression profiles are different from those in KS and PEL. It was reported that viral lytic genes; v-IRF-1 and v-IL-6 and ORF59 (a polymerase processivity factor, PF8) as well as a latent gene; LANA were expressed, suggesting that not a few cells in MCD are in the lytic phase.

3.2 Primary effusion lymphoma (PEL)

PEL is a rare B-cell originated lymphoma, most of which are infected with KSHV and usually emerges in patients suffering from acquired immunodeficiency syndrome (Carbone and Gloghini, 2008) by human immunodeficiency virus-1 (HIV-1) infection. PEL, used to be called body cavity-based lymphoma (BCBL), has been differentiated from the other lymphomas based on a *sine qua non* etiologic agent, KSHV. This rare lymphoma does not form a solid mass and is spreading along the serous membrane as PEL initially rises in one serous cavity such as a pleural cavity and a peritoneal cavity.
Cytologically, it is supposed that the tumor cells are derived from postgerminal center B cells and show a large cell immunobalstic plasmacytoid lymphoma and anaplastic large cell lymphoma and display a non-B, non-T phenotype (Brimo et al., 2007).
70 percent of PEL cases were co-infected with Epstein-Barr virus (EBV) in vivo (Ascoli et al., 1998). However, tightness with KSHV/HHV-8 infection suggests that KSHV/HHV-8 should have an important role for PEL pathogenesis with no doubt, taking into consideration that PEL frequently loses EBV but not KSHV after in vitro establishment of PEL cell lines.
Analyses on gene expression profiles of this rare tumor would give us a lot of information on how PEL was formed (Naranatt et al., 2004; Uetz et al., 2006) and we also analyzed three types of typical lymphocyte-originated tumor cell lines-primary effusion lymphoma (PEL) cell lines, T cell leukemia cell lines (TCL), Burkitt lymphoma (BL) cell lines and two sets of normal peripheral blood mononuclear cells (PBMCs)-in order to know how PEL was generated by searching characteristic gene expression profiles (Ueda et al., 2010). As a

result, these cell lines showed respective typical gene expression profiles and classified into clear four groups, PEL, TCL, BL and normal PBMCs. Two B lymphocyte-originated tumor cell lines, PEL and BL cell lines, clearly exhibited distinct gene expression profiles, respectively, which could be consistent with the fact that each was originated from different B-cell stages. KSHV seemed to govern the gene expression profile of the co-infected cell line, even though PEL is often co-infected with EBV in vivo and there was only one line that was co-infected with both KSHV and EBV. This suggests that existence of KSHV promotes PEL formation but not BL. Gene expression profiles of PEL were also distinct from those of KS, suggesting that cell environment affects a gene expression pattern. These data suggested not only that established typical tumor cell lines showed a distinct gene expression profile but also that this profile may be governed by a certain virus.

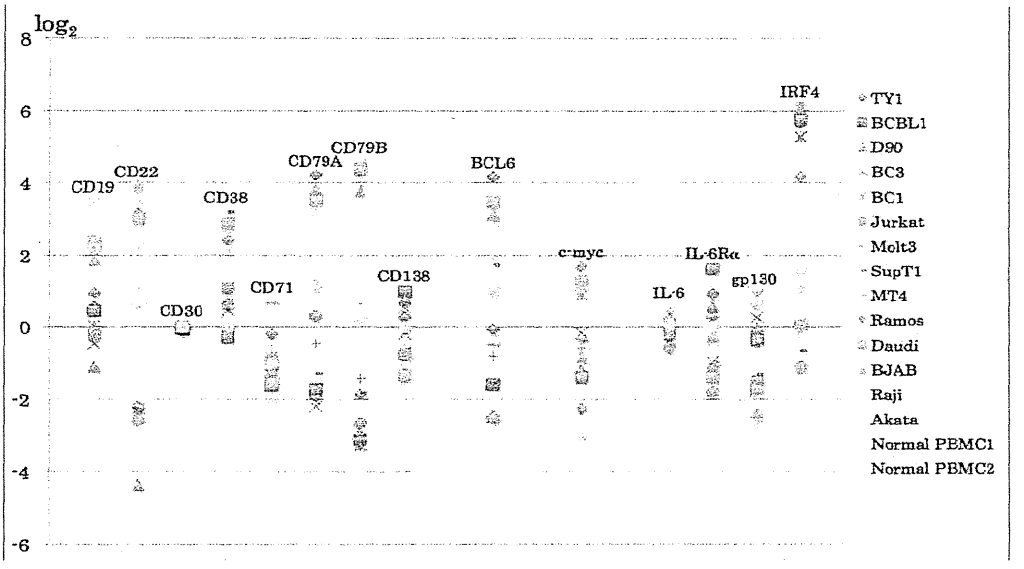

Fig. 3. Typical genes expression levels in PEL, BL and TCL

About sixty genes were prominently expressed in PEL cell lines, including Angiopoietin 1 (Ang-1, NM001146)), methyl CpG binding protein 1 (MBD1, NM015845), interleukin 2 receptor β (IL2Rβ, NM000878) and so on, compared with the other cell lines. The Ang-1 receptor, TIE-2 was not increased in PEL cell line, meaning that an autocrine loop could be unlikely but Ang-1 expression might take an effect in the AIDS environment. CD79A, B and BCL6 were remarkably reduced in PEL cell lines as reported (Du et al., 2002). CD138 (syndecan), CD22 and interferon regulatory factor 4 (IRF4) were relatively higher and CD38 and CD71 were lower in PEL cell lines and might reflect the difference between *in vitro* and *in vivo* (Fig. 3). c-myc was certainly higher in BL as BCL6, and IL-6 expression level was not so different but IL-6 receptor genes seemed to be more expressed in PEL and therefore, sensitivity to IL-6 could be higher in PEL.

4. Conclusion

It is very difficult to talking about viral oncogenesis, since we do not have a useful system for observation of the virus infection to pathogenesis, especially for high host-specific viruses. And our DNA array data suggest just that tumor cells show typical gene

expression profiles after establishment of PEL cell lines at an RNA level and it is may be very difficult to account for viral pathogenesis only by gene expression profiles. Furthermore, lytic gene expression should be taken into consideration to understand how PEL is formed and thus, it would be meaningful to find what kinds of gene were typically induced in lytic induction and for much better understanding, convenient viral infection to oncogenesis models in which we can observe continuously.

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